PHARMACOGNOSY AND PHYTOCHEMISTRY

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Week 5

Lecture 25

Drugs Containing Alkaloids (Part 3)

Hello everyone and welcome to the NPTEL course in pharmacognosy and phytochemistry. In this week we are learning about potent compounds called as alkaloids which are alkali like nitrogen containing. In the previous sessions we sought what are alkaloids and We saw the different classes of alkaloids and we have learned a few examples of alkaloids. To recall, we have learned tropane alkaloids from belladonna.

We have learned different different alkaloids such as opium. Now, in this session, we learn three more examples of alkaloid containing drugs, which are cinchona, which contains quinine. ephedra which contains ephedrine and vasaka or commonly referred to as adulsa which contains the alkaloid vasacine.

Cinchona

Synonyms: Cortex Cinchonae, Peruvian or Jesuit's bark

Biological Source: Cinchona is the dried bark of the stem or of the root of

- ***Cinchona calisaya*** Wedd.,
- ***Cinchona ledgeriana*** Moens.,
- ***Cinchona officinalis*** Linn., and
- ***Cinchona succirubra*** Pavon.,
- or hybrids of any of the first two species with any of the last two species, belonging to family Rubiaceae containing not less than 6.5% alkaloids.

Geographical Source: Andes. Bolivia and Southern Peru. Cultivated in Indonesia, Columbia, India, Guatemala, Bolivia, Ceylon etc.

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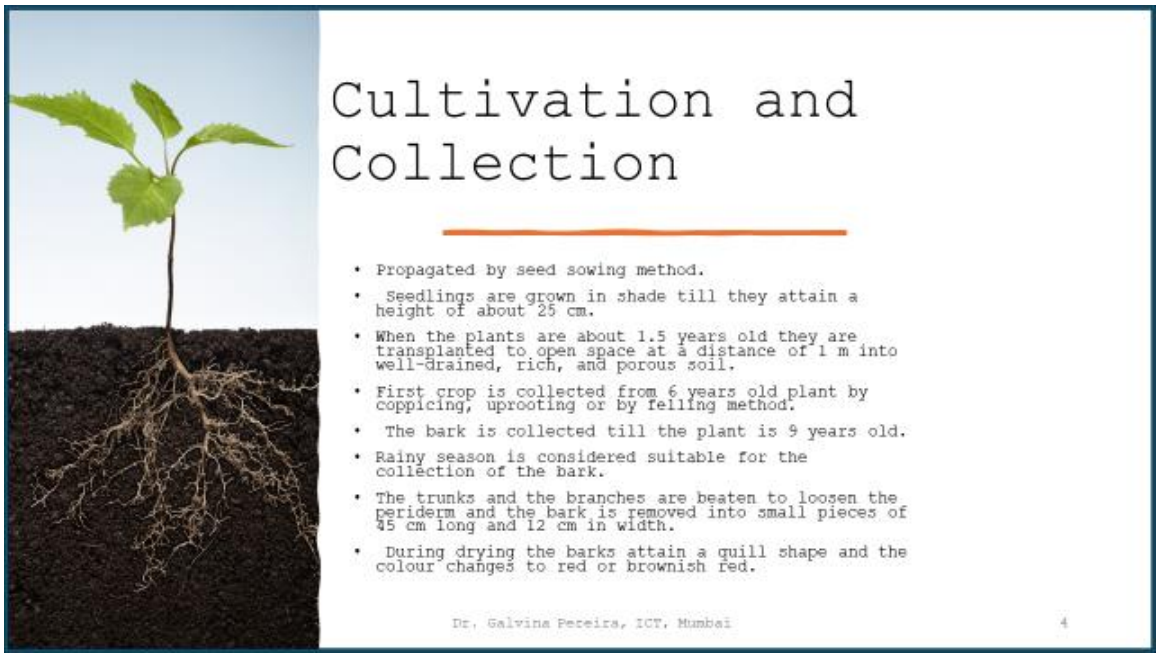
Let's start with the cinchona. Now cinchona has a very interesting story. Cinchona is a drug which was discovered in as early as 15th century. This has been used for its anthelmintic as well as antipyretic effects. It's also called as cortex cinchonae or Peruvian bark from natively where it occurs or Jesuit barks

which were the set of people who actually used the bark for their medicinal purposes. Now the name cinchona comes from the countess of cinchon who was cured by consuming this bark, the decoction of this bark. And hence, Linnaeus very rightly gave the bark the name cinchona. So, cinchona is the bark of many species of plants belonging to the genus Cinchona.

To name a few cinchona calisaya. cinchona ledgeriana, cinchona officinalis or cinchona succirubra. Now in some cases what happens is if you take the first two and then hybridize it with the next two that is officinalis and succirubra you get few more cinchona plant species and those are also being cultivated

So, geographically, they occur extensively throughout the world. They occur in the Andes, Bolivia, Peru; you will see them cultivated in Indonesia, Colombia. In India, we even have a quinine production plant, as well as in Guatemala, Bolivia, and Ceylon. So, these cinchona barks occur as quills—that is, they are dried and curved as quills or double quills.



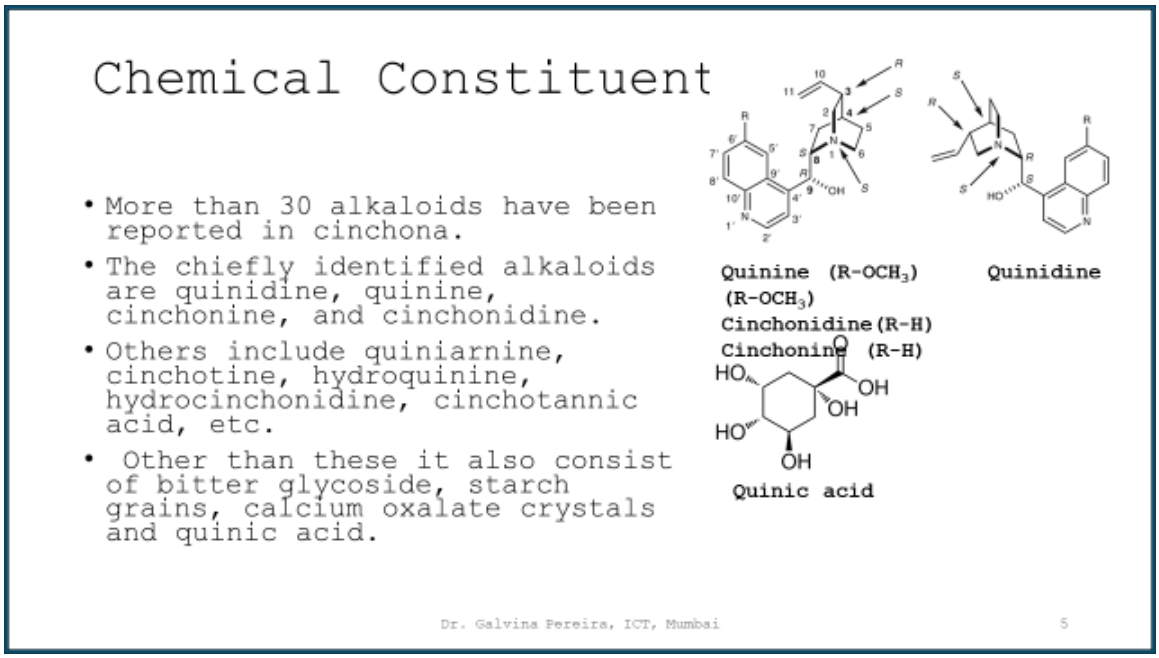
So, this is a very tiny seed, less than a half centimeter this is propagated mostly by sowing now this initial stages the seedlings are well protected from sunlight Because once they grow into trees, they are going to acquire a huge area. Now, taking into account their girth and their growth, a space of one meter is kept between each of these seedlings.

Now, first crop is taken as early as Six years later, and once they get old—or more than nine years old—it is seen that the content of quinine alkaloids, especially, goes on decreasing. Now we don't want a decrease yield and definitely after 9 years they are completely uprooted. Now rainy season is thought to be a best season for collection.

Mostly sometimes they were collected from old but now with the cultivation happening what is done is during the rainy season when the bark is little soft they are threshed or beaten to loosen from the periderm region and then pulled out. Now in some cases the plant is uprooted to get the root bark. The difference between the stem bark and root bark is generally in your market you get your stem bark with sizes as big as 30 centimeter in length whereas the stem root barks are tiny.

The root barks are approximately 5 to 10 centimeters in length so you can make out by length whether it's a stem bark or a root bark. Now Once you subject it to drying, the bark acquires a little curved or what is called as quill shape. It has tannins so it acquires a red or

reddish brown color. The stem bark also shows presence of fungus, lichens and those can be also used to identify whether the bark has been obtained from stem or root. Coming to chemical constituents, about 30 alkaloids have been reported in cinchona. It contains compounds such as quinine, quinidine. Now interestingly if you see quinine and quinidine structures are very much similar. The difference lies here at the 9th position.



So if you see here at the 9th position. The hydroxyl group acquires a R orientation whereas in this case it is an S orientation. Again if you go to see the 8 position with respect to hydrogen you can say this acquires an S position whereas in quinidine you will get an our position so that's a little difference otherwise structurally it's exactly the same it's just a little isomerism difference

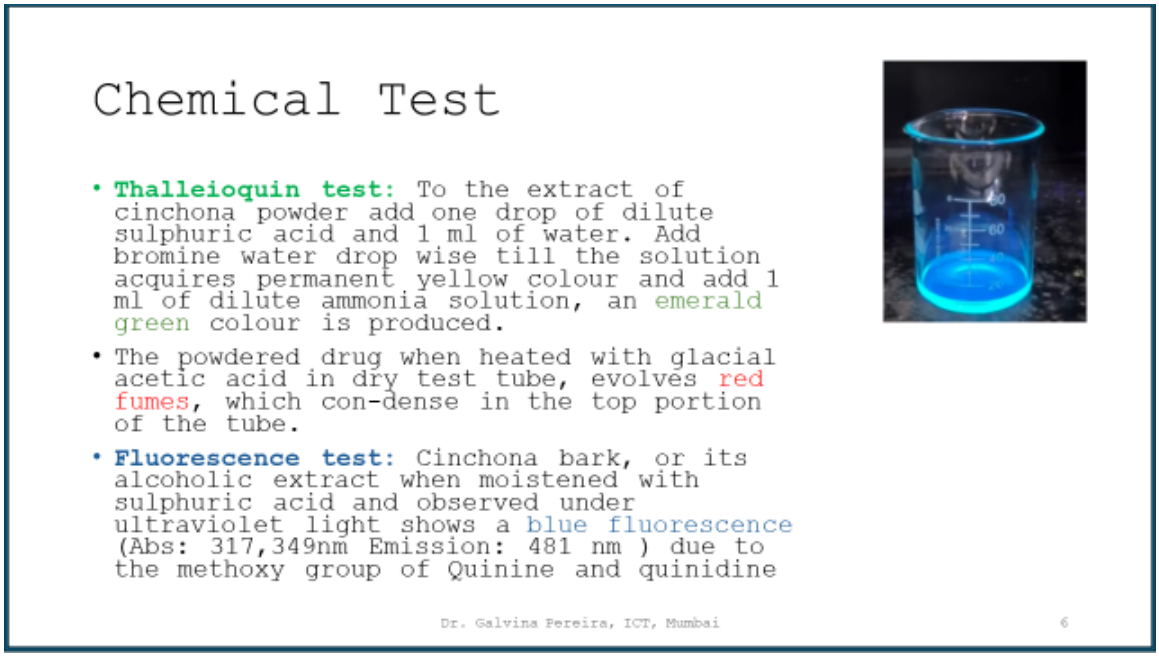
now this isomerism difference is also responsible for difference in activity while quinine it proves to be a very strong antipyretic and anti-malarial agent Quinidine is not as effective. In fact, it has more effects on heart or CVS. Now, if you just see this R group out here, that's the functionality in quinine and quinidine.

It's a methoxy substitution. Remove that and replace it with hydrogen. You get what is called as cinchonidin and cinchonin. Synchonidin and cinchonin in the same way are

isomers, but missing methoxy as compared to your quinine and quinidin. Apart from that, many other alkaloids are present.

This includes quinine iron, cinchotin, hydroquinine, hydrocinchonidin, And this is often found in complexation. Now, these are alkaloids. These are basic in nature. So they form associations with acids.

So two acids are predominantly seen in cinchonic acid. One is quinic acid and other is your cinchotannic acid. So these two acids often form complexes with your cinchona alkaloids. Now apart from that, it contains a few bitter glycosides, starch grains, and calcium oxalate as well.



Now it is said that the alkaloids are predominantly located in the parenchymatous part of the bark. Now if I have to check whether the cinchona bark contains these alkaloids, such as quinine, which are quinolone-type alkaloids. You can do a simple test called the thalleioquin test. Now what the thalleioquin test is: you extract cinchona powder in water or alcohol and add a drop

of dilute sulfuric acid and a little bit of a water or aqueous extract, well diluted, to that you can filter it to get the observations more clearly and go on adding drop by drop of bromine water. Now you will see that the solution changes its color a little bit to a more yellowish

tinge. When it changes to that yellowish tinge, you start adding a little bit of alkali, preferably ammonia solution.

When adding ammonia solution, approximately when you add a ml of it, you will see an emerald green color. This is a test for quinoline alkaloids. You can also do one more test: take a powdered drug and heat it with glacial acetic acid. In a dry tube, you will see red fumes emanating. These fumes condense quickly on the sides of the test tube and become more visible.

The interesting test you can see in cinchona is the fluorescence test. Now, the cinchona bark contains quinine and quinidine, and quinine and quinidine have the ability to fluoresce. What is fluorescence? Fluorescence is the ability of a compound to glow. Now, what exactly is glowing?

Glowing is basically absorbing a particular wavelength of light, and then, instead of emitting the same, emitting it at a slightly higher wavelength. In that case, what you get is a glow or fluorescence. Now, quinine sulfate has the ability to produce fluorescence. So, if you observe, it absorbs somewhere between 317 to 349 nanometers wavelength and emits at a higher wavelength, about 481 nanometers. This is mostly attributed to the methoxy group present, which we recently saw. So here what is done in this beaker is we have taken extract, alcoholic extract of cinchona bark and that alcoholic extract we have just added a drop of sulfuric acid. This is exposed to a UV lamp of about 365 nanometers and you can see quinine which is present in that produces an intense fluorescence. Now one interesting application of this fluorescence is sometime in your brewery, liquor industry where people prefer their brew such as beer to be a little bitter. In that case a little bit of quinine is added.

Now quinine is very bitter, so very dilute solution is added. So if you take your glass of liquor or beer and keep it under UV lamp, and if you get this kind of fluorescence, there's a good chance that quinine has been added, especially quinine sulfate has been added to increase the flavor or bitterness of the alcoholic drink. So application, the first and foremost application is anti-malarial because it has the ability to kill plasmodium, especially plasmodium falciparum, which is the main parasite responsible for malaria. Apart from that, it has analgesic, antipyretic, it kills microorganism due to its protoplasmic effect. It is

intensively bitter and hence considered as bitter stomachache and tonic. Now quinidine, which we saw, is an isomer of quinine.

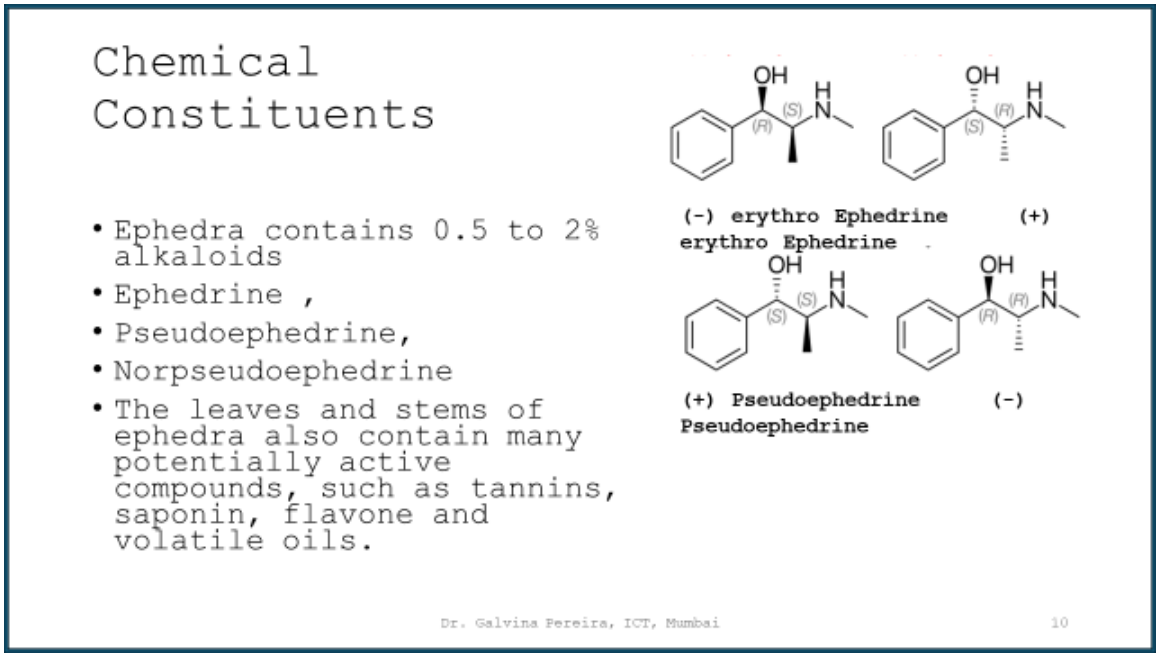
Like I said, apart from its structure, it gives an entirely different set of activities that is on the CVS. So quinidine is a cardiac depressant and cinconidine, if you go to see, is mostly used in rheumatism and neuralgia. Quinine hydrochloride is very bitter and has a bitterness value close to 2 lakh. Now what does that mean a bitterness value of 2 lakh? If I take a gram of quinine and dilute it 200,000 times, I will still be able to perceive the bitterness of quinine in that particular solution. So imagine, even this dilute solution of quinine can be bitter, and hence, in different methods of evaluation, quinine sulfate is often used as a bitterness standard. Now, moving on to the next drug. Our next drug is a xerophytic drug called ephedra. It grows in the Himalayan belts, mostly in the Chinese region, and it's synonymously called Mahuang.

Now, ephedra is the dried aerial parts, predominantly the stem, because this is a xerophytic adaptation. So the stems acquire a green color. They have chlorophyll, and the leaves are barely present in sets of two. in some cases 3 or 4 but very rarely at the nodes and it has different species which are used in medicine If you go to see the Indian perspective, the ephedra from India comes from Ephedra gerardiana and Ephedra major, whereas if you see the Chinese side, you can get mostly ephedra belonging to Ephedra sinica, Ephedra

equisetina, and in some cases, Ephedra nevadensis is also present. All of them belong to the family Ephedraceae. Like I said, it grows in the Himalayan tracts. So you can see it growing right from China, Nepal, India, Pakistan, Bhutan, to Turkey.

So this region, this is, you know, adapted to very dry and xerophytic conditions. You will see a drug like thin stems which show a shriveled appearance. Now, depending upon the species of ephedra, the thickness of the stems may vary, and the distance between the nodes will also vary.

Now, being a xerophytic shrub, it barely grows about half a meter to two meters in height. Mostly, it's cultivated in autumn for the reason that it has a very good content of alkaloids in it, and during the autumn season, you will see that the Twigs are nice, green, and slender. So once the plant or the aerial parts are picked, they are packed loosely in bags, and during the packing, some of them break, and you will see tiny twigs when you see the drug of commerce. Now, in terms of chemical constituents, it contains about 0.5 to 2% alkaloids, chiefly belonging to what are called protoalkaloids. If you see here, there are examples of phenylethylamines that we discussed last time. So this is the phenylethyl, that is 1 and 2 for ethylamine derivative.



So in phenylethylamine, we have ephedrine. Now, this occurs optically in different forms. So here you have a minus erythroephedrine. Here there is a plus ephedrine or plus erythroephedrine where you can see both of the substituents, hydroxy and methyl here, are above the plane, and here, if you go to see, both are below the plane.

Now, pseudoephedrine is a case where one of the functionalities is above the plane and one is below. So if hydroxy is above, methyl is below, and if methyl is above, hydroxy is below. You call it pseudoephedrine. So here you have a positive pseudoephedrine. With an SS configuration, and here you have a negative pseudoephedrine with an RR configuration.

Now, norpseudoephedrine is a derivative of pseudoephedrine in which the methyl group is absent. So, you remove this and just replace it with hydrogen. What you are going to get is norpseudoephedrine. So apart from that, it also contains other compounds: tannins, saponins, flavones, as well as, in some cases, little traces of volatile oil.

Now, being xerophytic, if you carefully do a transverse section, you will see adaptations such as a lot of chlorophyll in the stem and typically sunken stomata. Now, to evaluate this drug, we can do a few chemical tests. Take a little drug, boil it in water to create an aqueous extract. To that aqueous extract, just add a drop of dilute hydrochloric acid and a drop of copper sulfate solution.

Mix it well and let it cool. Heat for some time, and then, on cooling, add your sodium hydroxide in large excess—about 2 ml—and you will see that this liquid turns purplish or violet in coloration. Now to this if you add any organic solvent such as ether and shake vigorously, this purple color is transferred to the ethereal layer,

and the aqueous side or the aqueous layer becomes slightly blue. In terms of applications or uses of ephedrine, the advantage is you need not inject it. You can orally consume it, and still, it gives you much-desired effects. So, it is used as an anti-allergic, especially in hay fever. It is used as an anti-spasmodic and anti-edematic.

It is a decongestant, cough suppressant, stimulant, and a vasoconstrictor. So, It is also used to treat angina. Pseudoephedrine also shows almost similar activities as a decongestant and

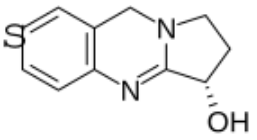
cough suppressant. Nor-pseudoephedrine is mostly used as a peripheral vasodilator to treat angina.

Now, ephedrine has the ability to stimulate heart rate, increase BP, promote bronchodilation, and exhibit very pronounced effects on the CNS because of its ability to bind with adrenergic receptors. Pseudoephedrine, as I said, has similar effects but fewer CNS effects compared to ephedrine.

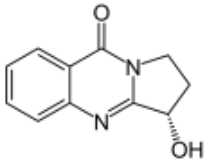
Now we move on to the third drug, and the third drug we use in the Indian system of medicine is referred to as Adulsa or vasaka or also as Malabar nut.Now what we do is we take the leaves of this plant. That is Justicia adhatoda or Adhatoda vasaka. It's a member of the Acanthaceae family. This plant grows mostly throughout the tropical regions of Southeast Asia and reaches a height of 2 to 4 meters. It bears beautiful white to pinkish flowers and tiny capsules containing seeds upon maturation.

Chemical constituents

- Alkaloids, tannins, flavonoids, terpenes, sugar and glucosides.
- Leaves composed of major constituents which are vasicine and vasicinone
- Other alkaloids present include vasicinol, adhatonine, and adhavasinone
- The flowers of this plant contain β-sitosterol-D-glucoside, kaempferol.



Vasicine



Vasicinone

Coming to the constituents, it contains quinazolin-type alkaloids, and the most important one among them is vasicin. Vasicin is the compound responsible for the antitussive effect provided by Adulsa. Now, this vasicine, when exposed to light, gets slowly oxidized and converts into vasicinone. So you will see plant contains vasicin as well as vasicinone or even if you purify vasicin, over time, due to oxidation, it readily converts into vasicinone. Hence, Adulsa syrups are mostly stored in amber-colored bottles to protect them from light. Apart from that, it contains flavonoids, terpenes, certain sugars, as well as glycosides. Now other alkaloids which are present include vasicinol, adhatonine and adhavasinone. The flowers, whitish or pinkish in color, are known to contain a sitosterol, specifically beta-sittosterol glycoside, as well as a flavonoid called camphorol.

In terms of applications, Adulsa has been traditionally used for many years in the Ayurvedic system of medicine to treat cough, asthma, fever, and in some cases, tuberculosis. Its extract is used to treat piles, jaundice, or even bleeding gums. It is mostly used as an expectorant. It is effective in treating cold and rheumatism.

It also alleviates bronchial, asthmatic, or pulmonary afflictions. Additionally, it is combined with other drugs for its antimicrobial, hepatoprotective, and antioxidant properties. It has been traditionally used, though the mechanism is unclear, to treat leprosy

and certain blood disorders. At slightly higher doses, it has a mild sedative effect. But yes, it also shows antispasmodic and anti-inflammatory effects.

It can show anti-diabetic effects. On some research scales, it has been proven. It also has anti-ulcer properties and is moderately hypotensive. So, thank you everyone for your patient listening. Here are a few references if you wish to know more about this drug.

Thank you.