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Safety of some of the Iiyiyiu healing plants*

Purpose

In this study, Teresa Tam looked at whether the healing plants are safe to take, and whether they are safe to take along with western diabetes drugs. (The 17 plants she looked at are listed at the end of this paper.)

To assess if the plants are safe to take, Teresa's study looked at two main questions:

1. Are the plants likely to affect a person's heart?
   If so, do they do this when taken alone? Do they do this if you take them along with a western diabetes medicine?
2. Do the plants affect the enzymes in our body that handle diabetes drugs? If they do, it could be dangerous to take the plant medicines along with western ones.

These kinds of tests are standard for any western drug. However, many plants and natural remedies have never been tested in this way.

Testing if the plants could affect people's hearts

The cells in our heart are always squeezing and then going back to normal, like a sponge. This is what makes our heart beat. Some drugs and foods make our hearts beat faster or slower by affecting this squeeze-and-release cycle. Obviously, a drug that changes your heart rate can be dangerous. So it is routine to check how any medicine affects heart rate. In this part of her study, Teresa tested four of the Iiyiyiu healing plants—sheep laurel, juniper,

* This is a plain-language version of an MSc thesis by Teresa Tam titled *The effects of Cree anti-diabetic natural products on drug metabolism and cardiomyocytes*. The thesis will be submitted to the Faculty of Medicine at the University of Ottawa in Fall of 2008.

diamondleaf willow, and lowbush cranberry. These were the four that seemed most likely to affect the heart or to react with other drugs.

For these tests, Teresa added plant extracts (tea) to heart cells from baby rats in a lab dish. The purpose was to find out:

- How strong a dose you can take before it starts to damage heart cells
- Whether the plants raise or lower heart rates (that is, if they affect how the cells squeeze and release)
- Whether they raise or lower heart rates if you take them along with one of the standard diabetes drugs (Metformin).

How strong a dose is safe for the heart?

First, Teresa looked at how much plant extract she could add before the heart cells got damaged or died. This told her something about how much would be safe for a person to take. That is, it told her the highest safe dose. She found that

- Juniper and sheep laurel would be safe for the heart. No human could take so much juniper that it would damage their heart cells.
- Diamondleaf willow could damage the heart, but only if a person took a very large overdose.
- Lowbush cranberry could damage the heart. It should not be taken often or in large amounts.

Do the plants affect heart rate?

Once she knew the highest safe dose for each plant, she checked if this dose would affect how fast or slowly the heart cells beat. Why use the highest dose for these tests, instead of a normal dose? Because we want to be sure these plants are safe even in a worst-case scenario—such as a person taking too high a dose by mistake. Fortunately, even at high doses, none of these four plants changed how fast the heart cells beat.

Do the plants affect heart rate if you take them along with Metformin?

What happens if you take one of the healing plants along with a western drug to lower blood sugar? Would the two drugs together change your heart rate? To find out, Teresa tested lowbush cranberry along with a common diabetes drug called Metformin (Glucophage).

Most of the time, it seemed to be safe for the heart to use both lowbush cranberry and Metformin. There were some signs that the two drugs together might affect heart rate, but this only happened at higher doses than any person would ever take. Still, we should be extra careful, because when people have diabetes their hearts are already under stress. Ideally, we should repeat this test using diabetic heart cells rather than healthy heart cells. Teresa tried to produce diabetic-like heart cells in the lab so she could do this test, but did not succeed.

To sum up, two of the plants were safe for the heart. One—lowbush cranberry—was not safe, and one was questionable. At normal doses, none of these four plants affected heart rate.

Testing if the plants are safe to take with other drugs

About how we absorb plants and other medicines

When we eat food or medicines, things called *enzymes* help us digest them. There are many different enzymes. But some drugs or foods interfere with one or more of these enzymes. Suppose a person is taking two different drugs for their diabetes: if the second drug interferes with the enzymes that the body needs to digest the first, the person could get harmed. The same thing could happen if a person uses drugs and healing plants together. The plant could change the amount of drug that a person absorbs.

However, most enzymes are quite specialized—they only act on certain foods or medicines. And we already know which enzymes act on the various western diabetes drugs. So if we can find out which enzymes the plants do and don't interfere with, we can predict which western medicines they might interfere with. In this part of the study, Teresa tested all 17 plants with ten different enzymes. She did these tests in a lab dish, not on live animals or people.

Do the plants interfere with important enzymes?

It turns out that several of the plants do interfere with these enzymes—at least in the lab. In fact, some of them hinder the four enzymes that are most involved in handling western diabetes drugs. So there is definitely a risk that some of the plants will not go well with certain western drugs.

However, the results are a bit different for each plant and enzyme. Teresa's paper describes which enzymes each of the 17 plants acts on. In future, we will be able to compare the enzymes a plant acts on to the ones a particular drug uses. This will help us avoid prescribing plants and drugs that interfere with each other.

In the meantime, the results tell us some interesting things about mixing the healing plants and western drugs:

- Several plants (tamarack, showy mountain ash, sheep laurel, juniper, and stag's horn club moss) affect two enzymes called CYP2C8 and CYP2C9. These two enzymes also handle some of the drugs used to lower blood sugar and fight heart disease. We may need to be careful about using these plants along with some of these drugs.
- Most enzymes are specialized, but there is one exception: an enzyme called CYP3A4 helps digest over half the drugs on the market. This includes several of the drugs used to treat high blood pressure, heart

disease, and kidney problems. Many of the Iiyiyiu plants do affect this enzyme and a related one. We may need to be careful with

  - Labrador tea
  - black spruce
  - showy mountain ash
  - jack pine
  - marsh Labrador tea
  - sheep laurel
  - juniper
  - diamondleaf willow

- Three plants (pitcher plant, balsam poplar, and lowbush cranberry) did not interfere much with any of the enzymes. These would probably be the safest ones to take along with western drugs. On the other hand, Labrador tea is probably the least safe to combine with western drugs. It seems to have a strong effect on a lot of different enzymes.
- Labrador tea and sheep laurel affect one enzyme in ways that might improve diabetes. This could be helpful if the plants are used alone and not along with a western medicine.

Which ingredients in the plants produce these effects on the enzymes? We don't know yet. But because the team recently identified the ingredients in some of the plants,[*] we are now in a position to guess. We can look at the plants that affect a specific enzyme and see if they are all high in one particular ingredient.

Do the plants just hinder the enzymes or do they actually use them up?

Although the Iiyiyiu plants may hinder the enzymes, they don't put them completely out of action. This would be much more serious, because it can

[*] See the article by Ammar Saleem and others called "Fingerprinting different plants in the Heath family."

take our bodies a few days to make new enzymes. Only one plant—balsam fir—shows any sign of actually using up the enzyme so it can't handle other drugs. Until we know for sure if this happens, people who are taking certain drugs for high blood pressure, heart disease, or kidney problems should avoid taking balsam fir everyday.

Can the plants be taken with blood-pressure medicines?

Many people with diabetes also have high blood pressure. So it is important to know if the plants can be taken along with blood-pressure medicine or not. Teresa checked three of the plants with Enalapril, a blood pressure drug that gets digested by enzyme CYP3A4. The three plants she chose were Labrador tea, speckled alder, and pitcher plant. None of these three plants interfered with Enalapril in any of her tests.

Conclusion

This study suggests that several of the healing plants could have harmful effects on people with diabetes. They could damage the heart, or they could affect the enzymes we use to digest other drugs. These results led Teresa to take a closer look at a few of the plants. Yet this closer look did not find any bad effects on the heart. Nor did she find bad effects when she put some of the plants together with western drugs for diabetes or for high blood pressure.

Recall that Teresa looked at two types of risks: effects on the heart, and effects on enzymes. Some of the plants that were higher-risk for the heart were low-risk for enzymes, and vice-versa. So it's hard to make blanket statements about which plants are safest. The risk would depend partly on whether the person was using a plant alone or taking it along with western drugs. It would also depend on exactly which plants and drugs the person was taking.

Appendix: list of plants that the study looked at

Plant name	Part of plant used
Labrador tea	Leaves
Balsam fir	Bark
Tamarack larch	Bark
Black spruce	Cones
Showy mountain ash	Bark
Speckled alder (gray alder)	Bark
Pitcher plant	Leaves
Jack pine	Cones
Marsh Labrador tea (northern Labrador tea)	Leaves
Sheep laurel	Leaves
White spruce	Leaves
Juniper	Fruit
Diamondleaf willow	Bark
Stag's horn club moss (ground pine)	Whole plant
Balsam poplar	Bark
Creeping snowberry	Leaves
Lowbush cranberry (mountain cranberry, lingonberry)	Fruit