Reports from the anti-diabetic plant project*

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CIHR Team in Aboriginal Anti-Diabetic Medicines

Scientific Committee Meeting
CIHR Team in Aboriginal Anti-Diabetic Medicines
Montreal, February 2011

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CONFIDENTIAL: Please note that this report is only intended for review by participants in the Anti-diabetic Plant Project. It contains confidential liiyiyiu traditional knowledge and confidential results from the academic researchers. A public report will be made once the information has been reviewed by the researchers, the elders and the communities.
A question is being asked right now in the Cree Board of Health: what use is research to the mission of the health board which is to provide services? It is a valid question to continually ask.

Thinking about the Anti-diabetic plant project, one thing that this project has done is provide about seven years of meetings where people from all communities have sat down two or three times a year to discuss traditional medicines (TM). Prior to that, were any groups talking about TM outside of the Elders’ Councils? The project has helped to broaden this discussion, which was one of the reasons that the Mistissini Elders’ Council wanted it in the first place.

This project showed that it is not difficult for a clinic within the Cree Board of Health to give patients access to their traditional system of care at the same time as providing western care. The Cree Board of Health did not provide the traditional care – that was done by the Healers with support from the Cree Nation; but the clinic encouraged people to choose the type of care they preferred. The clinic then helped patients to use both systems safely. The initiative in Mistissini is showing that patients can
choose to use one or both systems, and the Cree Nation and the local clinic can work together to give patients that access.

The researchers played an important role in this new process of collaboration. They addressed the concerns of the Healers about potential interactions between TM and western medicines. They also provided valuable feedback on how the plants may work in the body, to address the Healers’ main concern that Cree TM be used safely and effectively. They also explored how TM plants respond to being picked in order to help understand responsible and sustainable management of the resource.

The Cree Board of Health is currently reorganizing services in the clinics. The new approach aims to provide services that respond to the needs of the population, and the Board has identified a Cree approach to services as the cornerstone of that change.

Diabetes is one of the major, if not the greatest, health problem in every community in Eeyou Istchee. We need all the resources of the territory working together to meet this challenge. As diabetes is a new disease, when the project began in 2003, the effectiveness of TM was not generally known. The Anti-diabetic Plant Project proved that TM are...
extremely effective to prevent the onset of diabetes and to reduce its symptoms and complications. And in doing so, it has highlighted the important role that TM and Eeyou Healers have to play in helping to make our communities healthy.

All of the publications, local reports and documents from the anti-diabetic medicinal plant project are available on the project website which can be found at http://www.taam-emaad.umontreal.ca/ or through http://www.creehealth.org. Because of the complex approval process within the project, many of the documents are not yet available to everyone. For now, this current report will remain confidential within the project and in the confidential section of the website because it mentions aspects of traditional and scientific knowledge which may not yet have been approved by the healers and elders and made public by the scientists. Later it will become available on the main website.

If you wish to know more about the overall project please contact: Nadine Methot, the project’s administrative coordinator at (902) 446-2461 or antidiabetic-trad-med@pharmco.umontreal.ca. If you want to speak to someone about the Putting
Traditional Medicines First Mistissini project, please call Francis Awashish at (418) 923-3355 or at francisawashish@hotmail.com. You are also invited to contact Jill anytime at (514) 953-8283 or at torrie.jill@ssss.gouv.qc.ca.

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A. Report for the Cuerrier lab
(January 2011)

LOOKING AT HOW A PLANT’S STRENGTH VARIES WITH WHERE IT GROWS
Michel Rapinski’s project looks at how the strength of Labrador tea and pitcher plant changes depending on how far north the plants grow. During the summer of 2010 he collected samples of these plants from seven places (Whapmagoostui, Wemindji, Eastmain, Nemaska, Mistissini, Waskaganish, and Ottawa).

He has been trying to perfect the lab tests that he will use to see if where the plants grew affects how well they help cells take in sugar.

PREPARING A BOOKLET ABOUT ALL THE PLANTS
Michel has also been working on the booklet that will summarize information about the 19 plants. So far, we have summarized the information from our journal articles. Next, we need to add the information the Elders and Healers shared with us. At this meeting, we would like to talk with the community representatives about this booklet. We have questions like: What format would people like?
Should the booklet be public, or only for people involved with the project? Should the information be summarized for use in teaching materials?

Now that Michel has received approval to work in Wemindji, he will return there later this year to talk with the Elders and other interested people.

**Looking at how harvesting affects Labrador tea populations**

- Youri has been studying how much Labrador tea and pitcher plant you can collect before you damage the populations. For Labrador tea, we tried three different harvest methods:
  - Leaving the plants untouched (control)
  - Taking just the old leaves
  - Taking all the leaves

We harvested this way in 2008, and again in 2009. The idea was to simulate intensive harvesting. Each year, we counted the number of leaves on the plants, how big their stems were, how much they had grown, and how many flowers they had. That allowed us to compare how the plants were doing, depending on how heavily we’d harvested.

We found that taking all the leaves really damaged the plant. Most of these plants died after the second
year of harvesting, and the ones that survived had fewer leaves and grew less well. Taking just the old leaves was less harmful. It did not kill the plant or slow its growth badly, but it did slow it down a bit. It would probably be OK to take just the old leaves from a plant if you only did it every second year. Fortunately, Labrador tea is widespread across the north, so even if you harvest selectively, there will still be a good supply.

Looking at how harvesting affects pitcher plant populations

We did similar studies with purple pitcher plants. We found that when you remove pitcher plants, you actually get more new plants the next year than you otherwise would, because you’ve made space for the new ones. Nonetheless, the population depends heavily on mature plants surviving — pitcher plants can live for up to 50 years. When we took more than two plants in 10, the sites had still not recovered four years later.

We put our findings into a computer model to help us predict what would happen over time based on what we had observed in 2008–2010. Our computer model said that even if you used a “sensible” approach (collecting only mature and non-flowering plants) and took just one plant in twenty each year,
you would still kill off the population within 100 years. However, you could sustainably take:

- 5% (one plant in twenty) every two years
- 10% (one plant in ten) every five years or
- 20% (one plant in five) every ten years (see Figure 1).

If instead of the “sensible” method you used a “take everything” method, you would have to be much more careful. Taking more than one plant in five would eventually kill off the population, no matter how many years you left between collections. But you could probably harvest this way every three years if you only took one plant in twenty.

The healers use the whole plant in their remedies, so we too collected the entire plant. However, our observations lead us to believe that taking just the leaves would have less impact on the populations. We are starting a study to look at this.

This is a simplified summary of a more technical report from the Cuerrier lab.
B. Report for the Arnason lab
(January 2011)

The people in this lab have been working on various methods of identifying and describing the ingredients in the plants.

Brendan Walshe-Roussel (PhD student)

Brendan has been looking at how some plants reduce inflammation. He is focusing on black spruce, because this had the strongest anti-inflammatory effects of the Cree plants we tested. Brendan is trying to find out what ingredients are in black spruce, and which of them fight inflammation. He and honours student Baillie Redfern have been dividing black spruce’s ingredients into groups, and testing each group to see if it fights inflammation. If it does, they divide that group into smaller groups, and so on until they narrow down to individual ingredients.

Brendan is also writing an article on how the 17 Cree plants have different effects on inflammation depending on whether you mix them with water or ethanol. He has tentatively identified some of the ingredients in the plants for this work, but plans to re-check his results with a more exact test.
Ammar works on developing better tests for our project. So far, he has developed and published tests for 11 of the 17 Cree plants. He is now working on the remaining ones. One of the tests he developed allowed us to look at how the ingredients in Labrador tea and marsh Labrador tea vary with the season. An article on this has now been accepted for publication. Ammar also worked on the best methods for testing Anna Baillie’s samples of Showy mountain ash and American mountain ash.

Ammar and Carolina are still working on a test to be used with plants that protect nerve cells. We are trying this on pitcher plant, which has some ingredients that protect nerve cells in lab dishes. But to work well in live animals, these ingredients need to move from the stomach up to the nerve cells in the brain after an animal or human eats the plant. Our new test can already detect even tiny amounts of these ingredients in the brain, so it will tell us if the ingredients are getting where they need to be.
Jonathan is looking at the many plants in the blueberry and cranberry family that help fight diabetes. Some of these plants grow in Eeyou Istchee, and some grow in other parts of Canada or in other countries. Jonathan is applying our new method to “fingerprint” all of these plants. This will help us to identify the plants, and tell us if the different types share some family characteristics. He is now working on an article that describes this work.

Michel Rapinski (MSc Student)
In our earlier tests, we had found that Labrador tea and pitcher plant both help fight diabetes. We think that the plants that have the largest proportions of active ingredients will have the most effect. So
Michel is trying to find out what makes a plant high in active ingredients. He is using plants that were collected at four or five different latitudes (that is, further and further north). So far, he has been working mainly on Labrador tea. He expected that the further north the plant grew, the more active ingredients it would have. But his tests are showing the opposite: the more southerly plants seem to be stronger in active ingredients.

Jose Antonio Guerrero
(Post Doctoral Fellow)

Jose Antonio and Nan Shang (from the Haddad lab) have been looking at the ingredients in tamarack. They have now been able to narrow down to ten ingredients that all seem to have fat-fighting effects. These ingredients are from several different families of chemicals. One of them is completely new, which is exciting. The results will be put into a scientific paper.

Jose Antonio has also been able to identify three ingredients in black spruce that seem to be mostly responsible for the way spruce bark is able to fight...
“free radicals.” (Free radicals are particles that damage our veins and help cause heart disease and other problems.) This work was done with Cory Harris in the Johns lab. More plants and plant ingredients will be tested for their ability to fight free radicals.

Asim Muhammad (Post Doctoral Fellow)

Last June, the Elders said we should look at marsh Labrador tea, among others. Asim prepared the plant for testing, and divided its ingredients into eight groups. He passed the samples on to the Haddad lab, which tested the groups to see if they help cells to take in more sugar. The Haddad lab found that one of the eight groups did this. Now we are breaking that group down further, to try to identify its individual ingredients. San has also tested the groups to see if they might have an effect on the process by which our bodies turn some foods into sugar.

Articles Published or ready to be Published

Since our last report, two articles from this lab have been either published or accepted for publication:

1. José Á. Guerrero-Analco, Ammar Saleem, Padma Madiraju, Asim Muhammad, Tony Durst, Pierre Haddad, and John Thor Arnason. "Bioassay-guided Isolation of the Antidiabetic Principle from Sorbus decor (Rosaceae) used traditionally by the Eeyou Istchee Cree First Nation"
Isolation of the Antidiabetic Principle from Sorbus decora (Rosaceae) used traditionally by the Eeyou Istchee Cree First Nation.” This was published in the Journal of Natural Products.

The plain-language summary of this article was called “Identifying the active ingredients in showy mountain ash.”

2. Black P, Saleem A, Dunford A, Russell BW, Arnason JT, “Seasonal variation of phytochemical constituents, antioxidants and antiinflammatory activities of Northern Labrador tea Rhododendron tomentosum ssp. subarcticum.” This has been accepted by a journal called Planta Medica.

The plain-language summary was called “How the healing strength of Labrador tea varies with the season.”

ARTICLES BEING PREPARED
Jonathan Ferrier, Kimberly L. Colson, Joshua M. Hicks, Brian Killday, Sabina Trakić, Sulejman Redžić, Alain Cuerrier, Michael J. Balick, Alain Cuerrier, John T. Arnason. “Identification of Vaccinium spp. L. (Ericaceae) natural health products from North Eastern North America and Europe by nuclear magnetic resonance (1H NMR) spectroscopy.”
San Nguyen, Jose Antonio Guerrero, Ammar Saleem, Pierre Haddad, John Thor Arnason. “Aldose reductase inhibition by antidiabetic plants used by the Eeyou Istchee Cree First Nation.”

Asim Muhammad, Jose Guerrero-Analco, Padma Madiraju, Louis Martineau, Ammar Saleem, Pierre Haddad, and John Thor Arnason. “Isolation of the active antidiabetic principles of S. purpureae used traditionally by the Eeyou Istchee Cree First Nation.”

Brendan Walshe-Roussel, Carolina Cerniak, Ammar Saleem, Padma Madiraju, Asim Muhammad, Tony Durst, Pierre Haddad, and John Thor Arnason. “Phytochemical comparison of alcohol and traditional water extracts of antidiabetic plants used by the Eeyou Istchee Cree First Nation.”


for the analysis of phenolics in Rhododendron groenlandicum and Rhododendron tomentosum used by the Eeyou Istchee Cree First Nations for treating diabetic symptoms.

Jose Guerrero-Analco, Nan Shang, Ammar Saleem, Asim Muhammad, Lina Musalam, Brendan Walshe-Roussel, Alain Cuerrier, Pierre Haddad, and John Thor Arnason (2011). “Adipogenetic constituents from the bark of Larix laricina (Pinaceae), a valuable medicinal plant used traditionally by the Eeyou Istchee Cree First Nation.”

Staff Changes
San Nguyen has submitted his thesis and is working outside the university. Jon Ferrier was accepted into the PhD program. Michel Rapinski has moved from the Ottawa lab to the Cuerrier lab.

This text is a simplified summary of a more technical report from the Arnason lab.
that Salicortin helps mice gain less weight, store less fat in their livers, and have better insulin levels, but it does not lower their blood sugars directly. She still wants to do more comparisons of how Salicortin alone and balsam poplar work inside the mice's livers, muscles, and fat tissue. Then she will revise her existing article on balsam poplar and salicortin to include this new information.

**Studies of tamarack in mice**

Despina also did the same kind of tests using tamarack. In this study, tamarack helped lower blood sugars and improve how the mice's cells responded to insulin.
to insulin. In fact, the results this time were better than in the earlier study where Despina looked at whether tamarack could prevent weight gain and high sugars. As with balsam poplar, Despina wants to look more closely at exactly how the plant works inside the liver, muscles, and fat tissue. Then she will combine the results from this study and the one on prevention into a single article.

Speckled alder

The same kinds of tests on speckled alder suggest that it may have some effect on weight, and definitely improves blood sugars and insulin response. As with the preceding two studies, we still want to know exactly how the tree does this. Despina will put the results from this study into a third article.

Together, these three articles will form the core of her PhD thesis.
Meriem did the same kind of studies on mice as Despina to find out how Labrador tea produces its effects. She found that the mice that were given Labrador tea:

- Gained 6% less weight.
- Had lower levels of blood sugar (by 13%).
- Had lower levels of insulin in the blood (by 65%).
- Accumulated less fat in their livers (by 42%).
- As a result, their livers were less inflamed.

How does the plant do this? In the muscles, Meriem found that the plant uses the insulin path to increase the number of "trucks" (GLUT transporters) that carry sugar from the blood into the muscle. In the liver, it uses two different pathways: the insulin one, and another one that does not involve insulin. The plant seemed to act mostly on the liver and muscles; it had few effects on fat tissue.

Meriem submitted her master's thesis December 21, 2010. She has also written two articles that are now going through the review process:

1. "A combination of Catechin, Epicatechin and Quercetin underlies the in vitro adipogenic action of Rhododendron groenlandicum, an antidiabetic medicinal plant of the Eastern James Bay Cree pharmacopeia'' FRP-024-1-09

2. "Ingredients in Labrador tea that affect how our bodies store fat"
2. “Rhododendron groenlandicum, an antidiabetic plant of the Eastern James Bay Cree, attenuates insulin resistance in a diet-induced obesity mouse model” FRP-025-1-10. (The plain-language summary is called “How Labrador tea affects diabetes in mice.”)

We know that being obese raises people’s risk of getting diabetes. Yet one theory about diabetes says that it is partly caused by a person not being able to make enough fat cells to store all the calories they are taking in. Instead, some kinds of fats (called free fatty acids) accumulate in muscle cells and liver, and this helps create insulin resistance. According to this theory, things that help fat cells to reproduce and to store more fats would actually help with diabetes. Some of the standard diabetes drugs—including Rosiglitazone (Avandia)—work on this principle. So in a separate project, Meriem worked with people in the Arnason lab to try to identify the ingredients in...
northern Labrador tea that make fat cells store the “good” fats. This will be the subject of a third paper.

HODA EID’S STUDY OF HOW MOUNTAIN CRANBERRIES WORK INSIDE THE BODY

Even though Hoda finished her PhD last summer, she stayed on for a few months to finish looking at how mountain cranberries work. Her study, like the ones above, used mice that were fed a high-fat diet. In contrast to our earlier study, in this one the mountain cranberries did not help the mice to take off weight. But the current study used normal mice, while the earlier one used a special kind of mice—ones that have a genetic problem so their bodies don’t send them the usual signals to make them feel full and stop eating. Perhaps mountain cranberries only reduce weight in animals that have this particular type of appetite-control problem.

However, in the current study, mountain cranberries still did other good things:

• They lowered blood sugars (by 11%)  
• They reduced the amount of fat that got stored in the liver (by 44%)

Hoda’s tests showed that cranberries do this by using the insulin pathway to increase the number of
“trucks” that move sugar into muscles. In the liver, the plant uses both the insulin path and the other one to produce its effects. Hoda is now writing an article about this.

The journal turned down her earlier article on mountain cranberries, but she is revising it and will try again. (The article was titled “Vaccinium vitis-idaea, a medicinal plant of the Eastern James Bay Cree, mobilizes L6 muscle Glut4 transporters and exerts anti-obesity and antidiabetic effects in vivo.” The plain-language summary is called “Lowbush Cranberries as a way to fight weight and diabetes: results from some studies on mice.”)

CAROLINE QUELLET’S STUDY OF HOW TAMARACK AND BALSAAM POPULAR AFFECT THE WAY THE LIVER AND GUT HANDLE FATS

The Elders recommended that we look at tamarack and balsam poplar, and Lidia Nistor’s studies said the same thing. So now Caroline is looking at how these two trees affect the way our livers and guts handle fats and cholesterol. To do this, she is using the livers and guts from the mice in Despina’s study (described above). She is also looking at some other aspects of how fat gets made and carried into the cells. Caroline plans to finish her Master’s work in April 2011.
ABIR NACHAR’S STUDY OF HOW THE PLANTS AFFECT HOW MUCH SUGAR THE LIVER MAKES

Insulin and some other drugs help our livers to make less sugar, and store more of the sugar they do make. This lowers the amount of sugar that gets into the blood. Abir is screening all 17 Cree plants to see if they might do the same thing. Balsam fir seems to have strong effects on the liver, so Abir has been trying to find out which ingredients in balsam fir do this. She has been breaking the ingredients into smaller and smaller groups, and testing each group. She has found three ingredients that are very good at making liver cells produce less sugar and store more of it.

Abir has also been looking at 2 of the 11 ingredients that we separated out from pitcher plant (one of which is completely new). The first ingredient seems to have strong effects.

Abir transferred to the PhD program at the end of December 2010.
Like Labrador tea, tamarack seems to help fat cells to reproduce and to store fats that actually help with diabetes. So Nan has been trying to find out which ingredients in tamarack produce this effect. She has found a few of the ingredients responsible, one of which is completely new. However, her tests suggest that you get more effect from several of the ingredients acting together than you do from any one ingredient alone. Next, she will try to identify the best combinations, and then write an article about her study.

Another part of Nan’s project is to compare what happens when you dissolve the plants in water or in ethanol. She will be trying all 17 plants both ways, and testing if it makes a difference to how well the plants:

- make fat cells store the “good” fats
- help muscle cells to take in sugar
- help the liver to make less sugar or store more of it
Danielle Spoor's project on using math to understand all the results so far

Danielle has collected the results from all the studies the Anti-diabetic Plant Project has done, and put them into a large computer table. With help from Alain Cuerrier, she is using math to look for links between the different pieces. For instance, we might find links we hadn't thought of between the Elders' knowledge, the ingredients in the plants, and the plants' effects—both on diabetes itself and on the complications of diabetes. This may lead to new ideas about how and why certain plants work better than others. We also think this analysis will confirm our impressions about which of the plants have the strongest effects.

Charlotte Gauthier-Simard's study of how the plants affect hunger signals

The fat tissue in our bodies creates chemical messengers that play a role in telling us when we are full and also affect how our bodies handle insulin. (These messengers are called Leptin and Adiponectin.) Charlotte's project was to test all 17 plants to see if they make fat cells in the lab produce...
more of these messengers, or fewer. Unfortunately, there were some problems with the tests, so we did not learn about the messenger that controls appetite. However, we did learn about the one that affects how our bodies handle insulin. Of the 17 plants, balsam fir and white spruce seem to have the most effect on this messenger.

MICHEL RAPINSKI’S STUDY OF HOW LATITUDE AFFECTS THE INGREDIENTS AND STRENGTH OF LABRADOR TEA AND PITCHER PLANT

Past studies have found that plants that grow further north often have more healing effect. This may be because plants produce ingredients to help them withstand strong light, and plants that grow in the long northern days make a lot of these ingredients. Michel wanted to see if Labrador tea and pitcher plants had more of certain ingredients, and stronger effects, depending on how far north they grew. He collected samples of these plants from around five
1. “Inhibition of intestinal glucose absorption by antidiabetic medicinal plants derived from the James Bay Cree traditional pharmacopeia” by Δφση-βυ, b Λα. "Аδά" α_лα. "Аδά" 2010.

2. "Stimulation of AMPK and enhancement of basal glucose uptake in muscle cells by quercetin and quercetin glycosides, active principles of the antidiabetic medicinal plant Vaccinium vitis-idaea" by Δφση-βυ, b Λα. "Аδά" α_лα. "Аδά" 2010.


of the Cree communities. So far, he has the results for ingredients. It seems the plants do indeed make more or less of some ingredients depending on where they grow, but the more northerly plants don’t always have the most. Michel has now moved on to looking at whether the plant’s healing strength changes with where it grew.

UPDATE ON PUBLICATIONS

Articles that have been published since the last meeting

1. “Inhibition of intestinal glucose absorption by antidiabetic medicinal plants derived from the James Bay Cree traditional pharmacopeia” by Δφση-βυ, b Λα. "Аδά" α_лα. "Аδά" 2010.

Articles that have been published since the last meeting

1. “Inhibition of intestinal glucose absorption by antidiabetic medicinal plants derived from the James Bay Cree traditional pharmacopeia” by Δφση-βυ, b Λα. "Аδά" α_лα. "Аδά" 2010.


2. “Fat-fighting potential of speckled alder and balsam poplar” by D. A. and G. B. (Planta Med. 76:1439-46; 2010). The plain-language summary of this article was called “How lowbush cranberry works to lower blood sugar levels.”
6. “Rhododendron groenlandicum, an antidiabetic plant of the Eastern James Bay Cree, attenuates insulin resistance in a diet-induced obesity mouse model” by Ouchfoun, Brouard, Vallerand, Musallam, Arnason, Haddad. The plain-language summary of this article was called “How Labrador tea affects diabetes in mice.”

7. “Vaccinium vitis-idaea, a medicinal plant of the Eastern James Bay Cree, mobilizes L6 muscle Glut4 transporters and exerts anti-obesity and antidiabetic effects in vivo” by Eid, Brouard, Ouchfoun, Vallerand, Musallam, Arnason, Sweeney, Haddad. The plain-language summary of this article was called “Lowbush cranberries as a way to fight weight and diabetes: results from some studies on mice.”
NEW MEMBERS OF THE HADDAD LAB
Michel Rapinski arrived from the Arnason lab to finish his work on how growing location affects a plant’s healing strength.

DEPARTURES
Meriem Ouchfoun finished her Master’s thesis.
Hoda Eid finished the extra work for her project.

STUDENT PROJECTS/THESSES TO FINISH AFTER END OF FUNDING
Nan Shang: more laboratory work needed (enough to have material for two articles). Nan has a scholarship from China, but will also need some funds from the team (about $300/month).
Danielle Adiyiwola-Spoor: no more lab work needed. Must finish analysis of the computer table with Alain Cuerrier. Must then write up her PhD thesis.
Despina Harbilas: no more lab work needed; must write up her PhD thesis.

This is a simplified summary of a more technical report from the Haddad lab.
In this lab, we look at how the plants affect the complications of diabetes. (This means the illnesses that are caused by diabetes, or that often go along with it.) In particular, we are looking at the illnesses that happen when high blood sugar damages the nerves—either the small nerves in our feet, hands, and eyes, or the nerve cells in our brains.

Carolina Cieniak has joined the lab to look at how pitcher plant affects complications in mice that are predisposed to diabetes. The first step in these tests is to make mice pre-diabetic by giving them moderate, constant doses of sugar. Carolina and Fida Ahmed have found that they can produce a pre-diabetic state by giving mice sweetened condensed milk every day for months. Their original idea was to make a group of mice pre-diabetic, and see if pitcher plant helped protect their nerve cells.

CHECKING IF PITCHER PLANT MIGHT PREVENT PRE-DIABETES OR DIABETIC COMPLICATIONS IN MICE
against the damage that high blood sugars cause. They were surprised to find that when they added pitcher plant to the milk, the mice’s blood sugars went back to normal—so there was no nerve damage to protect against. These mice have never become diabetic, and they are now five months old. This is exciting, but we still need to repeat the tests to be sure of what we are seeing.

Checking if Pitcher Plant Could Affect Other Diseases Caused by Nerve Damage

Other diseases besides diabetes also involve sugar damage to nerve cells. It seems that diabetes can make some of these other illnesses worse. For instance, some people think diabetes makes Alzheimer’s worse. So we tested pitcher plant on mice that had an illness similar to Alzheimer’s. We wanted to see if the plant would prevent high blood sugars in these mice the same way it did in pre-diabetic mice. Curiously, it did not. We are trying to figure out why the plant has different effects in these two situations.
Checking if pitcher plant could lower anxiety

People who have chronic diseases like diabetes or Alzheimer’s often feel very anxious. We wanted to know if pitcher plant might have calming effects in these situations. So we put mice in situations that would make them anxious, and checked if the plant helped. We did this with four different groups of mice:

- healthy mice
- pre-diabetic mice
- mice with an Alzheimer-like illness
- mice with both pre-diabetes and the Alzheimer-like illness.

So far, our results suggest that the plant helps mice to cope with moderate-stress situations (like exploring new ground or spending time in brightly lit areas). It doesn’t seem to help in high-stress situations like being around an unrelated mouse. We are doing more studies on this.
Looking at how the plants affect the
"messengers" in nerve cells

In these tests, we are focusing on what happens inside a nerve cell to set off the changes that end up damaging the nerve. Nerve cells contain several kinds of "messengers" that tell the cell to act in certain ways. We know that diabetes interferes with these messengers. This causes changes in how the nerve cell works, and we think those changes lead to nerve damage. We looked for damage to the nerve cells located in two different spots: the base of the spine, and the brain.

In our first set of tests, we looked at a special kind of nerve cell—nerves that connect to the spine. Damage to these specific nerves causes the tingling that some diabetics feel in their hands and feet. In these tests, we used mice taken from the Haddad lab’s studies. These were mice that had been fed a high-fat diet along with balsam poplar or tamarack. We wanted to see how the "messengers" in these mice’s nerve cells changed. We focused on two particular families of messengers. Camille Juzwik, an Honours student, has looked at some messengers that change when a mouse becomes diabetic. When you give the mice tamarack, these messengers go
back to normal. But balsam poplar does not have this effect.

Fida Ahmed is doing the same kind of studies, but looking at how Labrador tea affects nerve cells in the brain. The Haddad lab did a study in which they fed mice Labrador tea at three different doses. Fida is now looking at the brains from these mice to see what happened to some of the “messengers” in their brain cells.

This is a simplified summary of a more technical report from the Bennett lab.
E. Report for the Johns lab
(December 2011)

Recall that “free radicals” are particles that damage our veins, and that people with diabetes make more of them than usual. Plants, foods, and medicines that fight free radicals are called “antioxidants.” The Johns lab has been looking at antioxidant effects of the Cree plants. The work focuses on three areas:

1. Identifying which ingredients in the plants are the strongest antioxidants
2. Finding out if key ingredients from the plants actually make it from the gut into our bloodstream, and from there to other parts of our bodies
3. Finding out if the plants protect against fatty liver disease, and the free radical damage that goes with it

Identifying Antioxidants in the Plants

A plant may have hundreds or thousands of ingredients. Cory and graduate student Gina Monk are trying to find out which ingredients are the best at fighting free radicals. They plan to look at as many
plants as they can before the end of the project. So far, they have looked at two of the best antioxidant plants: black spruce, and tamarack.

In black spruce, they identified the key ingredients in the bark that fight free radicals. Now they are looking at the ingredients in the cones. In tamarack, they found some ingredients that are very strong antioxidants. Interestingly, these are not the same ingredients as the ones that seem to help fight fat.

When we eat or drink any food or plant, it passes through the stomach and into the gut. From there, nutrients and other ingredients are absorbed into our blood, and spread to other parts of the body. But some ingredients do not get passed into the blood. It is important to know if an ingredient goes into the blood or not, because if it does not, it will probably not have an effect in the body. The Johns lab is working with the Arnason and Foster labs to try to measure whether specific plant ingredients get passed from the gut into the bloodstream.
Finding out if the plants protect against liver damage

When liver cells are exposed to some kinds of fat, they quickly develop large fat droplets inside them. Once the cells have a lot of fat inside them, they start to make more free radicals than usual. Patrick has been looking at how the plants act on fat and free radicals in the liver. He has found that:

- Many of the plants help to reduce the amount of fat in liver cells that have become too fatty. Balsam fir, tamarack, showy mountain ash, pitcher plant, jack pine, and northern Labrador tea all do this. Oddly, two plants—stag’s horn club moss and balsam poplar—have different effects depending on whether the liver cells are healthy or too fatty. These two plants lower fat in healthy liver cells. But in fatty liver cells, they actually make things worse.

- All of the plants help to prevent fatty liver cells from making more free radicals than usual.

How do the plants act to reduce free radicals? There are two possibilities. The plants might fight free radicals directly. Or they might encourage the cells to make more of other products that fight...
free radicals. One such product that a cell makes is called glutathione. Patrick and Nicola Grant (a new lab assistant) have been looking at what happens to glutathione levels when you add plant extracts. They have been doing this using both normal liver cells and fatty ones. Nicola is also trying to find a way to measure levels of the enzyme that is responsible for making glutathione.

Arvind has been looking at whether the plants affect how fatty liver cells respond to insulin. He and Patrick checked to see if the plants that are best at fighting free radicals are the same ones that help with insulin, but they aren't. They presented their findings at the 11th International Congress of Ethnopharmacology in Spain last September and won 2nd place for their poster.

This is a simplified summary of a more technical report from the Johns lab.
This lab tests the plant medicines for safety. We are at a stage where we are testing specific ingredients. We are looking at their structure (shape), which will help us to understand their properties.

- We began with an ingredient in black spruce called pungenin. When pungenin is eaten, our bodies break it down and change it in various ways, turning it into new kinds of ingredients. We are trying to see what these new ingredients might be and if they make the medicine more active and safe, or less so. So far, we have found six of these “breakdown” ingredients.

- We are also starting to look at rhaponticin, a major ingredient in tamarack bark extract. Other peoples have used rhaponticin to control allergies, thin the blood, fight inflammation, and fight diabetes. Like pungenin, rhaponticin gets broken down and changed inside our bodies.
Now we have begun to test what happens when you put pungenin, rhaponticin, or some of the other plant ingredients together with a western diabetes medicine. Will putting these medicines together cause them to break down into different ingredients than before? If so, this would also change the medicines’ safety. The western medicines we are using in these tests are Gluconorm (repaglinide) and Diamicron (gliclazide).

This work is progressing nicely. We have found that the “breakdown” ingredients of the western medicines do indeed change when they are put together with some of the plant medicines. So far, we have looked at how all 17 of the Cree plants affect the way our bodies break down Gluconorm. (We are also including a non-Cree plant, roseroot stonecrop, in our tests.) The results are much like the ones we found in our earlier studies of how the plants affect specific enzymes. That is, we still think that Labrador tea and Northern Labrador tea are the plants most likely to affect how western medicines work. And we still find that mountain cranberry is the least likely to affect western medicines.
The next step will be state-of-the-art studies of how the plants and medicines act on liver cells.

PRESENTATIONS AND OTHER PRODUCTS
1. Rui Liu will soon defend his Master’s thesis. (The plain-language version of Rui’s thesis was titled “Cree healing plants, Chinese plants, and western medicines: Are they safe to take together?”)
2. We have submitted an article to a journal for publication. The plain-language summary of this article was called “Testing if teas and some traditional medicines could interfere with western drugs.” The full title was Tam TW, Liu R, Arnason JT, Krantis A, Staines WA, Haddad PS, Foster BC. Cree anti-diabetic plant extracts display mechanism-based inhibition of CYP3A4. *Journal of Pharmacy and Pharmacology*, January 2011.
Putting Cree Traditional Medicine First Study: progress report

Traditional healing from the land is integral to Cree culture and many people regularly use locally available plants for treatments and healing. The researchers involved in the Anti-diabetic Plant Project found that some traditional medicine plants not only act to treat symptoms of diabetes but are also safe when combined with Western medicine.

Since 2009, a small, locally-controlled study has been on-going in Mistissini to assess using traditional medicines in diabetes care. Known as E Nikantaka’nuunch linuu Nita’kuyin (Putting Cree Traditional Medicine First), the project is investigating a more culturally-adapted approach to diabetes management in Eeyou Istchee.

Patients joining the study agree to follow a 6-month traditional treatment from one of the Healers while continuing their regular, clinical treatments. They give permission for the study to analyse the results of the blood tests they take every three months. Those enrolled receive their regular blood tests as well as some extra ones to assure safety.
In total, 49 participants registered to be part of the study. Of these, 24 are carrying through for the entire 6-month period, while 25 have stopped for various reasons: some never began, others travel frequently outside the community, a few had other health problems that were judged unsafe by the healers, and some did not take their medicines regularly.

Nine patients have already finished the six month study, and 8 of them have decided to continue using a combination of traditional medicines and Western medicines for their diabetes care.

The Cree Health Board is now analysing the results from the tests and these will be presented to the community partners who own the study. The testimonials of some participants with pre-diabetes have been very positive. They find that using traditional medicines has helped them to control their blood sugars. Collaboration between traditional healers, the local clinic, and patients with diabetes has been a positive experience in Mistissini and now the healers from Mistissini will be sharing their experiences with healers from other communities.

Karoline Gaudot
PCTMF Research Coordinator
Cree Nation of Mistissini
<table>
<thead>
<tr>
<th>Species</th>
<th>English Name</th>
<th>Cree Name</th>
<th>Southern Dialect</th>
<th>Northern Dialect</th>
</tr>
</thead>
<tbody>
<tr>
<td><em>Abies balsamea</em></td>
<td>Balsam fir</td>
<td>Inaasht</td>
<td>Δˊᵃ ᵃ  înåsh't</td>
<td>Δᵇ ᵃ ᵃ  hşıšht</td>
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<tr>
<td><em>Alnus incana subsp. rugosa</em></td>
<td>Gray alder</td>
<td>Atushpi</td>
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<td>Paper birch</td>
<td>Ushkui</td>
<td>Δⁿ ᵃ ᵃ  ushki</td>
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<td><em>Cladonia rangiferina</em></td>
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<td>Wapskamkw</td>
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<td>Eshjeemenan</td>
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<td>Δⁿ ᵃ ᵃ  aschimin</td>
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<td><em>Gaultheria hispidula</em></td>
<td>Creeping snowberry</td>
<td>Pieuaminaan</td>
<td>Δⁿ ᵃ ᵃ  piyeminânh</td>
<td>Δⁿ ᵃ ᵃ  piyaminh</td>
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<td>Δⁿ ᵃ ᵃ  wîpâshk</td>
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<tr>
<td><em>Juniperus communis</em></td>
<td>Ground juniper</td>
<td>Kakachiiminatuk</td>
<td>Δⁿ ᵃ ᵃ  kâhkâchîminâhtikw</td>
<td>Δⁿ ᵃ ᵃ  kâhkâchîminâhtikw</td>
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<tr>
<td><em>Leymus mollis</em></td>
<td>American dune grass</td>
<td>Weenibekushkushuh</td>
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<td>Δⁿ ᵃ ᵃ ᵃ ᵃ  winipakushkushuh</td>
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<tr>
<td><em>Lycopodium clavatum</em></td>
<td>Stag's horn club moss or ground pine</td>
<td>Pashtnahoagin</td>
<td>Δⁿ ᵃ ᵃ ᵃ ᵃ  pâschinâhkwâkan</td>
<td>Δⁿ ᵃ ᵃ ᵃ ᵃ  pâschinâhkwâkan</td>
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<tr>
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<td>Minihkw</td>
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<tr>
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<td>Δⁿ ᵃ ᵃ  iyâhtikw</td>
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<tr>
<td><em>Pinus banksiana</em></td>
<td>Jack pine</td>
<td>Ushchishk</td>
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<td>Kachichepak</td>
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<tr>
<td><em>Rhododendron tomentosum</em></td>
<td>Northern Labrador tea</td>
<td>Weeshichbuksh</td>
<td>Δⁿ ᵃ ᵃ ᵃ ᵃ ᵃ  wishipakush-k</td>
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<td>Pieuatikw</td>
<td>Δⁿ ᵃ ᵃ ᵃ ᵃ  piyâwâhtikw</td>
<td>Δⁿ ᵃ ᵃ ᵃ ᵃ  piyâwâhtikw</td>
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<tr>
<td><em>Sarracenia purpurea</em></td>
<td>Pitcher plant</td>
<td>Ayigadash</td>
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<td>Δⁿ ᵃ ᵃ ᵃ ᵃ  ayikatâsh</td>
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<tr>
<td><em>Sorbus decora</em></td>
<td>Showy mountain ash</td>
<td>Muskuminântuk</td>
<td>Δⁿ ᵃ ᵃ ᵃ ᵃ ᵃ ᵃ  miskuminâhtikw</td>
<td>Δⁿ ᵃ ᵃ ᵃ ᵃ ᵃ ᵃ  miskuminâhtikw</td>
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<td><em>Sphagnum fuscum</em></td>
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<td>Awashichishe</td>
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<tr>
<td><em>Stereocaulon paschale</em></td>
<td>Common coral lichen</td>
<td>Wâbuskamupâk</td>
<td>Δⁿ ᵃ ᵃ ᵃ ᵃ ᵃ ᵃ  wâbuskamupâk</td>
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<td><em>Thuja occidentalis</em></td>
<td>Cedar</td>
<td>Maastchik</td>
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<td>Δⁿ ᵃ ᵃ ᵃ ᵃ ᵃ ᵃ  mâschikw</td>
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<td><em>Typha latifolia</em></td>
<td>Cattail</td>
<td>Ushchikyoshkushu</td>
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<td>Δⁿ ᵃ ᵃ ᵃ ᵃ ᵃ ᵃ ᵃ ᵃ  wishipakush-k</td>
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<tr>
<td><em>Vaccinium angustifolium</em></td>
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<td>N'chiminatuk</td>
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<td>Δⁿ ᵃ ᵃ ᵃ ᵃ ᵃ ᵃ ᵃ ᵃ  nichkuminâhtikw</td>
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<tr>
<td><em>Vaccinium vitis-idaea</em></td>
<td>Mountain cranberry or lingonberry</td>
<td>Wishichimna</td>
<td>Δⁿ ᵃ ᵃ ᵃ ᵃ ᵃ ᵃ ᵃ ᵃ  wishichimnânh</td>
<td>Δⁿ ᵃ ᵃ ᵃ ᵃ ᵃ ᵃ ᵃ ᵃ  wishichimnânh</td>
</tr>
</tbody>
</table>

* not often mentioned during interviews

*Δ*: Northern dialect; *Δⁿ*: Cree dialect; *Δⁿⁿ*: Southern dialect; *Δⁿⁿⁿ*: English dialect.